INTERACTION BETWEEN NEUROTENSIN SYSTEMS AND THE STIMULANTS OF ABUSE, G. R. Hanson, Department Pharmacology & Toxicology, University of Utah, Salt Lake City, UT

The neuropeptide, neurotensin (NT) has been linked to extrapyramidal and limbic dopaminergic activity in what appears to be a reciprocating relationship. For example, the overall effects of NT on activated dopamine (DA) pathways is to antagonize the behavioral consequence; consequently, NT has been referred to as an endogenous neuroleptic. In addition, changes in DA receptor activity (i.e., D-1 or D-2 types) appears to alter the functional state of NT systems. Because of these interactions we tested the possibility that treatment with stimulants of abuse, such as methamphetamine (METH) and cocaine, altered NT pathways. The response by striatal and nucleus accumbens NT systems to both drugs was similar. Following treatment with high doses of either drug, the NT tissue content increased significantly by 12-hr, but returned to control by 24-48 hr. This effect was mediated principally by co-activation of D-1 and glutamate NMDA receptors. Studies which examined the mechanism were conducted with METH and revealed that large doses of this drug increased the expression of the NT/neuromedin gene. Using recently developed microdialysis techniques we observed that a low dose (0.5 mg/kg) of METH doubled striatal and accumbens NT release by D-2 mechanism, while a high METH dose (15 mg/kg) did not have an effect on release of this neuropeptide. The relevance of these findings will be discussed. (Research supported by grants DA 00869 and DA 09407)